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The association between leptin levels with glycemic control, body mass index, and progression of HbA1c values in type 1 diabetic children in Southwestern Saudi Arabia

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ABSTRACT

Background: Diabetes mellitus is a widespread serious metabolic disease with both short and long-term complications. Leptin is a polypeptide hormone, exclusively secreted from adipose tissue and its level is directly proportional to the amount of body fat. There was growing evidence that leptin level has an impact on insulin sensitivity, so this study aims to demonstrate the relationship between total plasma leptin concentrations with glycated hemoglobin, fasting glucose levels, and body mass index in diabetic children. **Methods:** A case-control study was carried out in the Najran University Hospital and included 133 type 1 diabetic children and 71 healthy controls in the same age group. In this due, plasma fasting blood sugar (FBS), HbA1c, and leptin were analyzed. **Results:** Significantly higher values of leptin in the diabetic group were seen in our study. In addition, leptin showed non-significant positive correlations with FBG in diabetic children ($r=0.110$, $p=0.359$). While, it revealed positive significant correlations with HA1c and BMI ($r=0.245$, $p=0.005$ and $r=0.393$, $p<0.001$ respectively) and a non-significant positive correlation with age ($r=0.64$ and $p=0.593$). **Conclusions:** Our results displayed that leptin in children with type 1 diabetes was significantly greater than what was seen in the normoglycemic control group. Moreover, leptin was correlated with HbA1c and BMI and this may explain the insulin implication in the secretion of leptin.

Keywords: Insulin; Type 1 diabetes mellitus (T1DM); Leptin; HbA1c; BMI

1. INTRODUCTION

Typically, diabetes mellitus (DM) is a prevalent serious metabolic disease. Out of approximately 20 million diabetic patients, diabetes mellitus type 1 (T1DM) is roughly constituting 5 % of the diabetic individuals and about 80 thousand newly discovered cases are diagnosed every annum. It is attributed to the ultimate insufficiency of insulin leading to severe hyperglycemia, with a high mortality rate if untreated (Friedman & Friedman, 2002; Gruessner & Gruessner, 2013; Margreiter et al., 2013). According to reports of the Ministry of Health in Saudi Arabia (Alotaibi et al., 2017), convergently 0.9 million individuals have been confirmed as diabetic cases in 1992, and this number had increased to reach 2.5 million people by 2010, constituting a 2.7-time increase in the typical incidence rates in less than two decennia. Leptin is a typical product of the ob gene, it is a polypeptide hormone-containing 167-amino-acid, exclusively secreted from adipose and its level is in direct proportion to the amount of the body fat (Zhang et al., 1994; Considine et al., 1996). It acts predominantly through connecting a specific receptor in the hypothalamic cells. The physiologic function of that hormone includes the suppression of appetite, the increase of energy expenditure, and consequently, the body weight regulation (Halaas et al., 1995; Pelleymounter et al., 1995; Campfield et al., 1995; Stephens et al., 1995).

Leptin exerts its metabolic effects on many organs including inhibition of the output of corticosteroids and glucagon, boosting glucose uptake, and repressing hepatic output of glucose. Deep perception of the leptin mode of action in lowering glucose levels might offer new plans for managing metabolic disorders (Anna et al., 2017). Leptin concentrations were diminished in newly diagnosed diabetic children and rise within 3–5 days after introducing insulin injection to become quite comparable to that found in normal non-diabetics. This is postulated to be attributed to a stimulatory effect of insulin on leptin production, nutritional replenishment, or both factors together (Hanaki et al., 1999). Therefore, this would represent additional evidence that insulin has a direct effect on leptin secretion independent of alterations in weight (Azar et al., 2002).

Leptin can increase the sensitivity to insulin in rodents' models of T1DM without any influence on the insulin level (German et al., 2010; Denroche et al., 2011). Independent of its impact on energy balance, leptin is crucially implicated in glycemic regulation and it might be useful as a therapy for other conditions. Leptin therapy was typically approved for lipodystrophy treatment and has glucose-reducing impacts in rodent models with either type of diabetes mellitus (Cummings et al., 2011). Hence, the main goal of our study was to set the relationship between total plasma leptin levels with body mass index (BMI), fasting glucose levels, and glycated hemoglobin (HA1c).

2. METHODS

This was a cross-sectional, hospital-based- case-control study that was accomplished in Najran University Hospital & King Khalid Hospital in Najran City- Southwestern Saudi Arabia from March 2015 to September 2020 (ethical approval number NU/MID/16/024-EC-10).

The study samples comprised 133 Saudi children (78 Male 58.6% & 55 female 41.4%) clinically diagnosed as T1DM as realized by some specialized Diabetes Association (Lin et al., 2002), and 71 healthy volunteers (42 males 59.2%, 29 females 40.8%) represented as a control group. The age of the study groups ranges from 4 to 14 years and both groups were age-matched.

Whole blood samples were collected from the fasting patients and control subjects in plain and EDTA tubes. Fasting blood sugar and glycated hemoglobin were measured by using cobas c 311, analyzer from EDTA whole blood and serum respectively. Serum leptin was assayed by ELISA, using kits from SUN LONG (CHINA). The BMI was simply measured from the formula (kg/m^2). The data was processed and analyzed using a statistical package for scientific and social studies (SPSS) version 21.

3. RESULTS

Out of 204 school-age and toddlers, 133 were diagnosed as T1DM (78 male and 55 female) and 71 healthy controls (42 male and 29 female) were enrolled in our study. The age of the study group ranged from 4 to 14 years. Our study revealed significantly higher leptin levels in the T1DM patients than in the healthy control subjects (256.7 ± 16.4 vs 45.2 ± 11.6 , $p < 0.0001$). The fasting blood glucose was typically higher in diabetic children than in healthy control (196.9 ± 56.3 vs 82.8 ± 8.4 , $p < 0.001$) whereas, BMI was as significantly as lower in diabetic patients than what seen in the healthy control group (17.5 ± 1.8 vs 18.1 ± 1.4 , $p < 0.009$). Moreover, the age was insignificantly different between the diabetic and healthy groups (10.2 ± 2.9 vs 10.7 ± 2.3 , $p < 0.223$) (table 1).

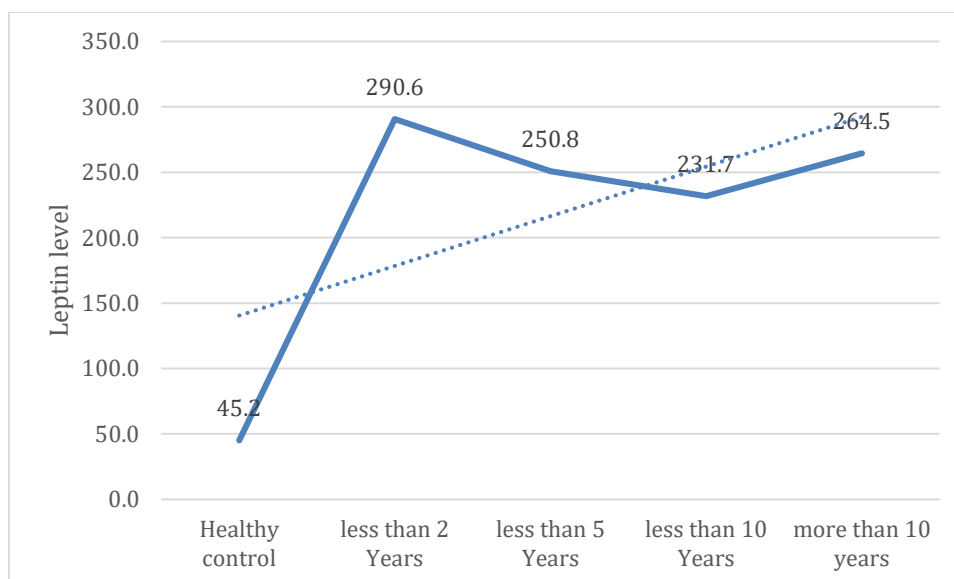
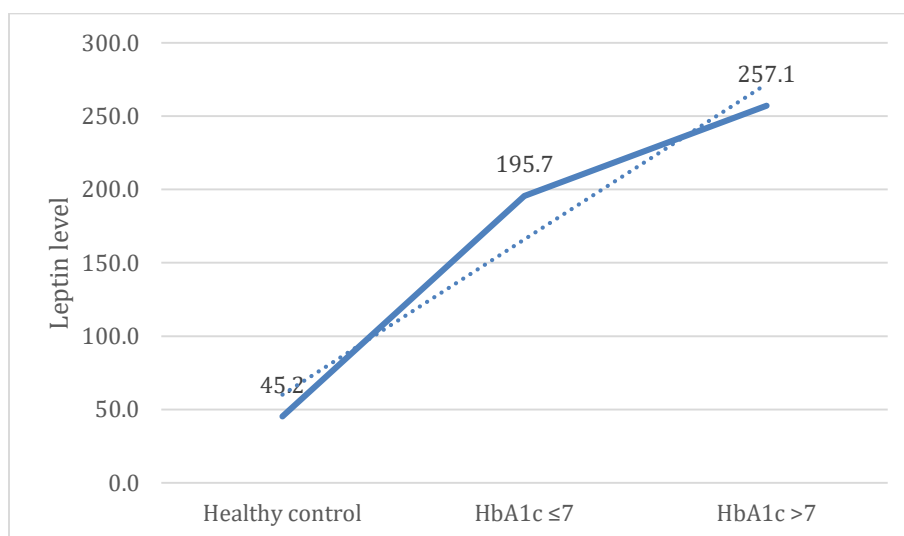
Leptin showed non-significant positive correlations with FBG in diabetic children ($r = 0.110$, $p = 0.359$). While, it revealed positive significant correlations with HA1c and BMI ($r = 0.245$, $p = 0.005$ and $r = 0.393$, $p < 0.001$ respectively) and non-significant positive correlation with age ($r = 0.64$ and $p = 0.593$) (table 2). Concerning the age sub-groups, leptin displayed a higher mean in diabetic school-age children and adolescents than in their corresponding control sub-groups. Leptin concentration according to the disease duration is shown in figure 1.

Table 1 Study results in diabetic and control groups

	Diabetic patients	Healthy control	p-Value
Leptin	256.7 ± 16.4	45.2 ± 11.6	0.000
FBS	196.9 ± 56.3	82.8 ± 8.4	0.000
BMI	17.5 ± 1.8	18.1 ± 1.4	0.009
Age	10.2 ± 2.9	10.7 ± 2.3	0.223

Table 2 Pearson Correlation of leptin levels with fasting blood sugar (FBS), BMI, and age in the studied groups

	Diabetic group				
Leptin	FBG	HbA1c	BMI	Age	Gender
r. value	0.110	0.245**	0.393**	0.064	0.42
p. value	0.359	0.005	0.001	0.592	0.01
	Healthy control group				
Leptin	FBG	HbA1c	BMI	Age	Gender
r. value	-0.028	0.356**	0.030	-0.013	0.101
p. value	0.749	0.002	0.737	0.879	0.08


Figure 1 Leptin concentration according to the duration of disease, p-value >0.001

Figure 2 Leptin concentration according to the progression of HbA1c values, p-value >0.001

The leptin level (mean \pm STD) for the diabetic patients with HA1c ≤ 7 is lower than in patients with HA1c > 7 (195.7 ± 225.5 and 258.6 ± 187.8). Overall, the two categories of HA1c in the diabetic children revealed significantly higher values of leptin than in the control (256.7 ± 16.4 vs 45.2 ± 11.6 , $p < 0.001$) (figure 2).

4. DISCUSSION

Since it has been increased in the developing world (Hossain et al., 2007), diabetes is a critical health problem as diabetic patients are at risk to develop both short and long-term complications as renal, cardiovascular, blindness, and diabetic septic food (Chen et al., 2011). Literature supposed that the leptin hormone plays a decisive role in the energy metabolism regulation and glycemic control, and is the main regulator for the equilibrium between food consumption and energy expenditure (Morton & Schwartz, 2011). Its activity decreases during the fasting state and starvation, while it increases in the well-fed state.

Our study showed significantly increased levels of leptin hormone in diabetic children than in the comparable healthy control ones. Leptin is typically an adipocyte-derived signaling hormone that is obviously implicated in carbohydrate metabolism and hence in energy balance and body weight regulation. Recent data displayed that depression in the rate of leptin mRNA expression is significantly linked with T2DM and could be a worthy non-invasive diagnostic and predictive marker for diabetes (Al-Harithy & Alomari, 2021).

Concerning gender, the association with leptin levels is mildly significant in diabetic children. Leptin hormone levels vary largely in adipocytes, certain factors may affect leptin levels in plasma. Some discrepancies in the literature that relate leptin hormone to diabetes mellitus, numerous studies found the leptin to be normal or elevated in T1DM patients (Verrotti et al., 1998; Hanaki et al., 1999; Kiess et al., 1998). It had been proposed that the alterations in leptin secretions and sensitivity may be engaged to some pathophysiological interaction with T1DM (Galletti et al., 2012; Pham et al., 2013; Musil et al., 2015). The finding that leptin level is positively linked to BMI in diabetic children is in concordance with that reported by Sitar-Taut et al., (2021) who concluded that diabetes and increased BMI are associated with variations in both leptin levels and leptin/kg/m² values. Since alterations are manifested even in overweight patients, this may propose a fundamental issue for early intrusion in diabetes when associated with obesity (Sitar-Taut et al., 2021; Samananda et al., 2021).

Another study revealed significant correlation being existed between leptin concentration and BMI in non-diabetic females. However, this finding is not rather significant in diabetic males and this could be attributed to the gender variations to the small sample of male participants in that study (Al Sheikh, 2017). Thus, gender could be typically considered as a significant determinant of serum leptin level in T1DM and this could be expounded by different body fat distribution and the rather higher resistance in females with T1DM when compared with that in diabetic males (Obradovic et al., 2021).

In addition, our study found a mildly significant correlation between the leptin hormones levels with HbA1c in children with T1DM and those with HbA1c values > 7 that is linked with higher leptin levels. Type 1 diabetes shares the same characteristics of insulin resistance, a property of T2DM or metabolic syndrome, and is recognized by high values of leptin hormone (hyperleptinemia) (Iacobellis et al., 2014). Chao and co-workers demonstrated that the glycosylated hemoglobin, HbA1c, value of the diabetic group was higher than the corresponding values in the non-diabetic group, and in the non-diabetic group, the HbA1c level was found to be elevated with bodyweight gain (Chao et al., 2021). For children and adolescents, another study found that HbA1c level diminishes every 100 percentiles from 2- to 4-year-old, progressively rises prior to puberty, when it peaks at 12- to 14-year-old, and then reaches the least concentration after the twenties (Pinhas-Hamiel et al., 2014).

Many factors could increase leptin levels such as diabetes duration, glycemic control, and daily insulin requirements (Iacobellis et al., 2014). Leptin hormone suppresses insulin synthesis and secretion and typically augments insulin sensitivity, as well as participates as a regulatory effector for fat and carbohydrate metabolism in muscle and liver (Amitani et al., 2013). Nevertheless, the glucose-lowering influence of leptin is being acquired with standard therapeutic insulin, and the true effect on glycemic index could not sometimes be contemplated (Zouhar et al., 2020).

5. CONCLUSION

Our study exhibited that leptin in type 1 diabetic children was significantly higher than in healthy children, this may due to insulin implicative role in the secretions of leptin. Moreover, leptin is clearly correlated with BMI and progression of HbA1c values.

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Author's contributions

Dr. Huneif: concept and design of the study, clinical studies, and supervision of the study.

Prof. Shalayel: manuscript preparation and literature search, and critical and final revision as well as final editing of the manuscript.

Dr. Elhussein: concept and design of the study, manuscript preparation and literature search, data acquisition, Laboratory investigations and carried out the initial and statistical analyses.

Dr. Fadlelseed, Dr. Elbadawi: manuscript preparation and literature search, data acquisition, and Laboratory investigations.

Dr. Hamid, Dr. Almedhesh, Dr. Seham, Dr. Abdulwahab Alqahtani, Dr. Alzahrani, Dr. Alshehri: data collection, clinical studies, Laboratory investigations, and revised the manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Najran University, Kingdom of Saudi Arabia (NU/MID/16/024-EC-10).

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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